1. **TRADE NAME OF THE MEDICINAL PRODUCT**

Etoposid "Ebewe"

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Etoposide 20mg/ml

3. **PHARMACEUTICAL FORM**
Concentrate for solution for infusion.

4. **CLINICAL PARTICULARS**

4.1. Therapeutic Indications
Etoposide is a antineoplastic agent for intravenous use. It can be used alone or in combination with other oncolytic agents.

Available data show that etoposide may be used in treatment of small-celled lung cancer, non-seminomatous testis carcinoma.

There is some evidence that indicate objective response in the palliative treatment of non-small cell lung cancer, in the reinduction therapy of Hodgkin's disease, in induction therapy of non-Hodgkin lymphoma and acute myelocytic leukaemia in children and adults and induction- and reinduction therapy of chorion carcinomas.

4.2. Posology and Method of Administration
Etoposid "Ebewe" is only administered by slow infusion (see below).

Etoposide concentrate for solution for infusion must be diluted before use (see section 6.6; Instructions for use and handling).

Adults: The recommended dose of Etoposid "Ebewe" is 60–120mg/m² i.v. per day for 5 subsequent days. As Etoposid "Ebewe" causes myelosuppression, the course of treatment must not be repeated more often than with intervals of 21 days. Repeated courses of treatment with Etoposid "Ebewe" infusion must not be given before the blood picture has been controlled for signs of myelosuppression and found satisfactory.

Paediatric patients: Safety and efficacy in children have not been established.

Elderly: Dose adjustment is not necessary.

Renal impairment: In patients with renal impairment but with normal hepatic function, the dose of etoposide must be reduced and haematological minimum values and renal function must be monitored.

Recommended dose regimen on the basis of creatinin clearance is as follows:

Creatinin clearance (ml/min)	Recommended daily dose (% of standard dose)
>50	100
15–50	75
<15	Contraindicated (see section 4.3 Contraindications)

The diluted solution for intravenous infusion prepared according to the instruction in section 6.6 should be administered by slow intravenous infusion over a period of at least 30 minutes. A facial flush is a sign of too rapid a rate of infusion.
Etoposide must not be administered by intra–cavitary injection.
Be careful in order to avoid extravasation.

4.3. Contra-indications
Etoposide is contraindicated in:
- patients who have shown hypersensitivity to the active ingredient or to any of the excipients.
- patients with severe hepatic dysfunktion.
- patients with severe renal impairment (creatinin clearance <15ml/min, see section 4.2 Posology and mode of administration)
- patients with severe myelosuppression.

4.4. Special Warnings and Precautions for Use
Etoposide should only be administered by health professionals experienced in the use of antineoplastic treatment.

Etoposide must not be administered intra-arterially or intracavitarily (pleura, peritoneum or other cavities).

When etoposide is given intravenously, care is advised in order to avoid extravasation.

If radiation and/or chemotherapy is given before initiation of etoposide treatment, an appropriate break must be made, to let the bone marrow regenerate.

If the leukocyte level falls below 2,000/mm³ or the thrombocyte level is below 50,000/mm³, the treatment must be discontinued until the blood cells again have reached acceptable levels (thrombocytes above 100,000/mm³, leukocytes above 4,000/mm³). Depending on whether etoposide is used alone or as combination treatment, the blood levels regenerate typically within 21 days. Peripheral blood counts and hepatic function must be monitored. (See section 4.8 *Undesirable effects*).

Bacterial infections must be brought under control before initiation of treatment with etoposide.
Close contact with patients recently vaccinated with poliovirus vaccine is to be avoided.

Anaphylactic reactions as flush, tachycardia, bronchspasm and hypotension may occur (see section 4.8 Undesirable effects).

Nausea and vomiting occur in app. 30–40% of the patients. Antiemetics are beneficial in control of the adverse reactions.

Etoposide should be administered with caution in patients receiving radiotherapy or chemotherapy and in patients with cardiac arrhythmia, a previous myocardial infarction, hepatic dysfunction, renal dysfunction, peripheral neuropathy, disturbance of micturition, epilepsy or brain damage or inflammation of the oral mucosa.

The occurrence of acute leukaemia, which can occur with or without a preleukaemic phase has been reported rarely in patients treated with etoposide in association with other anti-neoplastic drugs.

Etoposid "Ebewe" contains 260.6mg ethanol perml. At a dose of 120mg/m² etoposide, a patient with a body surface area of 1.6m² would receive 2.5g ethanol. This must be taken into account when etoposide is administered to patients with a history or alcohol abuse or in patients receiving *disulfiram*.
With respect to benzylalcohol content of Etoposide "Ebewe", it should not be administered to children younger than 6 months in view of the potential for metabolic acidosis developing.

Etoposide may have genotoxic effects (see section 5.3 Preclinical safety data). Men treated with etoposide are therefore advised not to make women pregnant during treatment and for up to 6 months after treatment. There is a possibility of irreversible infertility.

4.5. Interactions with other Medicaments and other forms of Interaction
Radiotherapy or the administration of drugs which cause myelosuppression may augment the myelosuppression induced by etoposide.

Etoposide may potentiate the cytotoxic and myelosuppressive effect of other drugs.

The effect of oral anticoagulants may be increased.

Phenylbutazone, sodium salicylate and salicylic acid may affect the protein binding of etoposide.

Cross-resistance between anthracyclines and etoposide has been demonstrated experimentally.

There are no data about administration of etoposide with drugs that are known to inhibit phosphatase activity (e.g. levamisol hydrochloride).

Potentially beneficial interactions
Etoposide is usually used together with other cytotoxic drugs and synergistic effects are assumed to occur, mostly expressed by cytotoxic effect. Such a synergy has been documented *in vitro* for certain drugs including methotrexate and cisplatin.
In animal models a synergistic effect on tumour cells has been shown for the following chemotherapeutic agents: cisplatin, carboplatin, mitomycin C, cyclophosphamide, BCNU, vincristine, dactinomycin and cytosine arabinoside.

4.6. Pregnancy and Lactation
Pregnancy: Safety in use of etoposide during pregnancy has not been established. Women of childbearing potential should be advised to avoid pregnancy. Caution is advised when prescribing to pregnant women (see section 5.3 Preclinical safety data)

Lactation: Etoposide should normally not be given to breastfeeding mothers.

4.7. Effects on Ability to Drive and Use Machines
Adverse reactions such as fatigue and transient cortical blindness indicate that cardriving or handling of machines cannot be recommended shortly after treatment with etoposide.

4.8. Undesirable Effects

Infections and infestations

Rare
Fever has been reported in rare cases during use of etoposide and sepsis has rarely been reported.

Blood and the lymphatic system disorders.

Very common:
The dose limiting toxicity of etoposide is myelosuppression, preferably leukopenia and thrombocytopenia. Anaemia occur rarely.

The lowest leukocyte value occur app. 21 days after treatment.

Rare:
The occurrence of acute leukemia, that may occur with or without a preleukemic phase, has rarely been reported in patients treated with etoposide in combination with other anti-neoplastic drugs.

Immune system disorders:

Uncommon:
Anaphylactic reactions characterised by shiver, flush, tachycardia, dispnoea, bronchospasm and hypotension have been reported after administration of etoposide. A higher frequency of anaphylactic reactions in children who received infusions in higher concentrations than

recommended, have been reported. The role the concentration of the infusion plays (or the infusion rate) in development of anaphylactic reactions, is uncertain. These reactions have usually responded on discontinuation of treatment and administration of pressor agents e.g. adrenalin (epinephrin), corticosteroids, antihistaminics or volume expanders if relevant.

Rare:
Fever has been reported in rare cases during use of etoposide and sepsis has rarely been reported.
Infrequently hypersensitivity reaction may occur due to benzyl alcohol which is present in Etoposid "Ebewe".

Very rare:
Two cases of Stevens-Johnson syndrome have been described in the literature; a connection with etoposide is not proven

Metabolism and nutrition disorders

Rare:
Hyperuricaemia has been reported in rare cases during use of etoposide

Nervous system disorders:

Common:
Peripheral neuropathy has been observed in 0.7 to 2.0% of cases.

Rare:
Affection of the central nervous system, including: confusion, hyperkinesia, somnolence, dizziness, fatigue, aftertaste and transient cortical blindness.

Vascular disorders:

Common
Hypotension may occur after too rapid infusion and may be reversed by lowering the infusion rate.

Uncommon
Hypertension and/or flush have also been reported. The blood pressure returns usually to normal level within a few hours after discontinuation of infusion.

Cardiac disorders

Very rare
Myocardial infarction and rhythm disturbances have rarely been reported after use of etoposide.

Respiratory disorders:

Uncommon
Apnoea with spontaneous resumption of breathing has been reported after discontinuation of etoposide treatment. Sudden, fatal reactions in connection with bronchospasms have been reported. Pneumonia have rarely been reported.

Gastrointestinal disorders:

Very common
Nausea and vomiting are the most common gastrointestinal toxicities and occur in app. 30–40% of the patients (see section 4.4 Special warnings and special precautions for use).

Rare:
abdominal pain, diarrhoea, constipation, anorexia, oesophagitis and stomatitis occur rarely.

Hepato-biliary disorders:
Etoposide has shown to reach high concentrations in liver and kidneys and presents hereby a possibility of accumulation in case of inhibition of function.

Uncommon
After high doses of etoposide, an increase in liver enzymes has been reported.

skin and subcutaneous tissue disorders:

Very common
Reversible alopecia that sometimes result in total baldness has occurred in app. 66% of the patients.

Rare:
Rash, urticaria, pigmentation and pruritus have been reported in rare cases after administration of etoposide.

Very rare
A single case of radiation recalled dermatitis has also been reported.

4.9. Overdose
Total doses of 2.4 to 3.5 g/m² administered intraveneously. over 3 days have resulted in severe mucosal inflammation and myelotoxicity. Metabolic acidosis and cases of severe hepatic toxicity have been reported in patients receiving higher doses of etoposide than recommended.

Tested antidotes against etoposide overdosage have not been established. Symptomatic and supporting treatment must be given.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties
Antineoplastic agents/podophyllotoxin derivatives, ATC-code: L 01 CB 01.

Etoposide is a semisynthetic derivative of podophyllotoxin with a significant cytotoxic activity. Etoposide affects the function of topoisomerase II (DNA opening enzyme) and inhibits hereby the DNA-synthesis in the terminal phase of the effect of topoisomerase. This results in cleavage of DNA single and double strings. Cell death occurs in relation to the concentration of etoposide and time of exposure. Etoposide is phase specific with cell stop in S and early G_2–phases of the cell cycle.

5.2. Pharmacokinetic Properties
The pharmacokinetic properties of etoposide underlies substantial interindividual variation. It is rapidly distributed and is bound to proteins by app 94% in human serum. Plasma decay kinetics follow a bi-exponential curve and correspond to a two compartment model. The average volume of distribution is app. 32% of body weight. Etoposide show a relatively bad penetration property into cerebral spinal liquid. App. 45% of an administered dose is excreted through urine, two third are excreted unchanged within 72 hours. Phenylbutazon, sodium salicylate and salicylic acid may affect the protein binding of etoposide.

5.3. Preclinical Safety Data
Reproduction toxicity: Etoposide is teratogeneous in rats at dose levels corresponding to the levels at clinical use.

Mutagenicity: Positive results from in vitro and in vivo tests regarding geno and chromosomal mutations caused by etoposide indicating that it is mutagenic, are available.

Carcinogenicity: Animal trials demonstrating the carcinogenicity of etoposide have not been performed.

However, based on the DNA damaging effect and the mutagenic potential, etoposide should be considered as potentially carcinogenic in humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Benzyl alcohol	Ph. Eur.
Ethanol	Ph. Eur.
Anhydrous citric acid	Ph. Eur.
Macrogol 300	Ph. Eur.
Polysorbate 80	Ph. Eur.
Nitrogen	Ph. Eur.

6.2. Incompatibilities
Etoposide should not be diluted in buffered solutions with a pH>8, because of the probability of a precipitate forming.

Should only be diluted with isotonic sodium chloride or isotonic glucose infusion solutions. The concentration of etoposide in the reconstituted solution for infusion should not exceed 0.4mg/ml due to the risk of precipitation.

6.3. Shelf Life
3 years.

6.4. Special Precautions for Storage
Chemical and physical stability after opening have been documented for 24 hours. From a microbiological point of view, the product must be used immediately. If the product is not used at once, the use of other storage conditions are in the responsibility of the user. The storage conditions must not exceed 24 hours at 2–8°C.

6.5. Nature and Contents of Container
1 vial of 2.5ml contains 50mg etoposide as active ingredient.
1 vial of 5ml contains 100mg etoposide as active ingredient.
1 vial of 10ml contains 200mg etoposide as active ingredient.
1 vial of 20ml contains 400mg etoposide as active ingredient.
1 vial of 50ml contains 1000mg etoposide as active ingredient.

6.6. Instructions for Use/Handling
Handle according to guidelines for cytotoxics .
Concentrate for solution for infusion must not be used undiluted.

7. MANUFACTURER
EBEWE Pharma Ges m.b.H. Nfg.KG
A–4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT
December 2003